Remarks

Claims 2-4 were previously pending in the subject application. By this Amendment, claims 2-4 have been amended and new claims 5-9 have been added. No new matter has been added by these amendments. Support for the amendments to claims 2-4 and new claim 7 can be found, for example, at page 2, line 18, and page 3, lines 6 and 17-28. Additionally, support for new claims 6 and 7 can be found, for example, at page 3, lines 4-8, and page 3, lines 9-15, respectively. Further, support for new claim 8 can be found at page 2 line 7 and support for new claim 9 can be found at page 2, line 30. Accordingly, claims 2-9 are now before the Examiner for consideration.

The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. The amendments should not be taken to indicate the applicant's agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Initially, the specification has been objected to because of an informality at page 3. By this Amendment, the specification has been amended at page 3, last paragraph, to include a period at the end of the sentence. The applicant thanks the Examiner for her careful review of the specification.

Claims 2 and 3 have been rejected under 35 U.S.C. §102(b) as being anticipated by Fasmer *et al.* (1987). The applicant respectfully traverses this ground of rejection because the cited reference does not teach each and every element of the claimed invention.

Fasmer *et al.* discuss the potency of nefopam, in its racemic and different enantiomeric forms, when treating pain in rats. The administration methods in this reference are intraperitoneal, intracerebroventricular, and intrathecal. These delivery routes are very different than the intranasal route contemplated by the current invention. Thus, there is no reason to expect that the compositions used by Fasmer *et al.* would be suitable for intranasal administration, as required by the amended claim 2.

Additionally, claim 2, as currently amended, requires the composition to be an aqueous solution with a pH between 4 and 7. Fasmer *et al.* make no mention whatsoever of the pH of the compositions used. Also, Fasmer *et al.* do not explicitly disclose that the compositions used are

aqueous solutions but rather just state that the nefopam is dissolved in 0.9% NaCl (see page 508, left column under "Animals and Drugs" section). The solvent is not revealed and could potentially be ethanol or another non-aqueous solvent. However, even if the solvent was assumed to be water, a 0.9 % NaCl saline solution would have a pH above 7 and would thus fall outside the pH range required by the claimed invention.

It is basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra; Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

Thus, it is well established that in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). As discussed above, Fasmer *et al.* do not teach a composition that is suitable for intranasal administration. Moreover, Fasmer *et al.* fail to disclose an aqueous solution with a pH in the range of 4-7. Accordingly, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Fasmer *et al.* reference.

Claims 4 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Fasmer *et al.* (1987) in view of Keller *et al.* (U.S. Patent No. 6,485,958). The applicant respectfully traverses this ground of rejection because the cited references, either alone or in combination, do not teach or suggest the claimed method.

As discussed above, Fasmer *et al.* teach that nefopam may help relieve pain in rats, when administered via intraperitoneal, intracerebroventricular, or intrathecal injection. Keller *et al.*

disclose a propellant-containing aerosol formulation that may or may not contain a pharmaceutically active compound. Keller *et al.* briefly mention that nefopam, along with an extensive list of other compounds, may be used in the aerosol formulation. However, Keller *et al.* give no indication that nefopam would be preferable to use among all the other compounds or that nefopam would be effective in a formulation for intranasal administration. Thus, there is no reason to combine the teachings of these references.

The predecessor of the Federal Circuit has opined, "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. See *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.' " See *In re Beattie*, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed Cir. 1992) (quoting *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). Finally, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Further, even if the cited references were considered in combination, and (+)-nefopam was selected, the composition would be an organic propellant-containing composition intended for direct administration to a site of damage. Keller *et al.* disclose that systemic absorption is to be avoided. By contrast, the present invention relates to a composition intended to treat a wide variety of pain conditions, including cancer pain.

Accordingly, the present invention does not address the same problem as the cited references. Rather, the present invention addresses the problem of achieving effective relief in cases where a patient is suffering considerable pain, such as cancer pain, requiring a systemic effect.

The solution to this problem is quite different from anything suggested in the prior art. Not only is a particular active agent selected, but the form in which it is presented and the intended site of action are quite different. Moreover, the results that are achieved by the current invention are very advantageous. Nefopam is rapidly and completely absorbed from the nasal cavity, and provides the rapid onset of action required to bring pain relief. Due to its high potency and selectivity, a lower dose of (+)-nefopam can be delivered by the nasal route, which results in lower C_{max} related side-effects for equivalent efficacy.

Currently, due to its high first-pass metabolism, racemic nefopam is delivered 3-4 times daily by the oral route. (+)-Nefopam has a longer duration of action by the nasal route. This means that (+)-nefopam can be a once or twice daily nasal product.

It has been well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield applicant's invention does not make the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125,1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art ..." *In re Dow Chemical Co.* 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969).

In this case, there is no suggestion of the desirability to use the NaCl-containing nefopam solution of Fasmer *et al.* in the propellant-containing aerosol formulation of Keller *et al.* The nefopam in the Fasmer *et al.* reference was injected into the abdomen, spinal cord, or brain of rats. Keller *et al.* discuss a wide variety of application methods of an aerosol formulation. Despite the very brief mention of nefopam among a long list of compounds in the Keller *et al.* reference, one of

ordinary skill in the art would have had no motivation to use a compound that was injected into the abdomen, spinal cord, or brain in an aerosol formulation that is sprayed in the nose. In addition, the administration methods are so different that one of ordinary skill in the art would not have had an expectation of success in using nefopam to relieve pain (such as cancer pain) via an aerosol spray.

Additionally, claim 4, as amended, requires that nefopam be administered as an aqueous solution with a pH in the range of 4 to 7. The deficiencies of the Fasmer *et al.* reference with regard to these requirements have been discussed above. Keller *et al.* do not teach that an aqueous solution is preferable, but instead mention that water can be used as a cosolvent in certain cases (see column 10, line 25). There is no suggestion of the desirability of an aqueous solution for use with any aerosol formulation, let alone one containing nefopam. This is yet another combination that one of ordinary skill in the art would have had to have made with no motivation to do so in order to arrive at the claimed method.

Furthermore, Keller *et al.* also make no mention whatsoever of the pH of any aerosol formulation contemplated for use. In fact, due to the use of dinitrogen oxide and ethanol in many of the discussed formulations, it is likely that the pH of any Keller composition would be greater than 7. Thus, the combination of the Fasmer *et al.* and Keller *et al.* references not only fails to teach a composition with a pH in the required range, it teaches away from it.

Due to the foregoing reasons, the combination of references fails to teach the claimed method. Accordingly, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

In view of the foregoing remarks and the amendment above, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicant also invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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